# *dynamic processes in cells (a systems approach to biology)*

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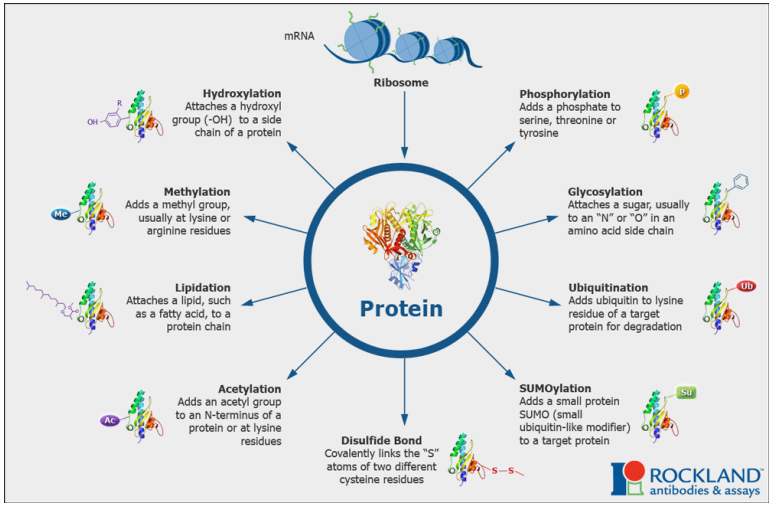
lecture 7

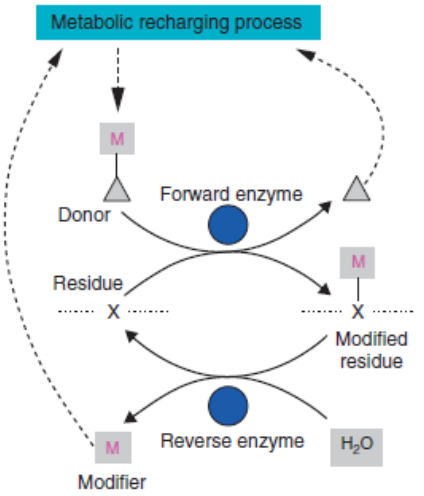
22 september 2016

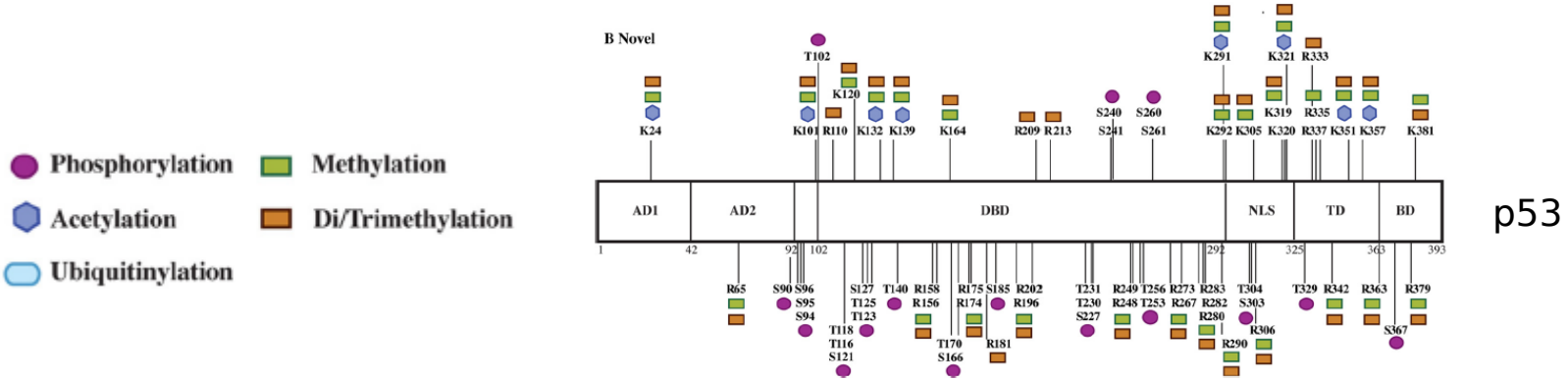
# weak linkage in molecular regulation – PTM

construct <u>new molecular states</u> having distinct functional properties

post-translational modification (PTM) by covalent attachment and energy dissipation



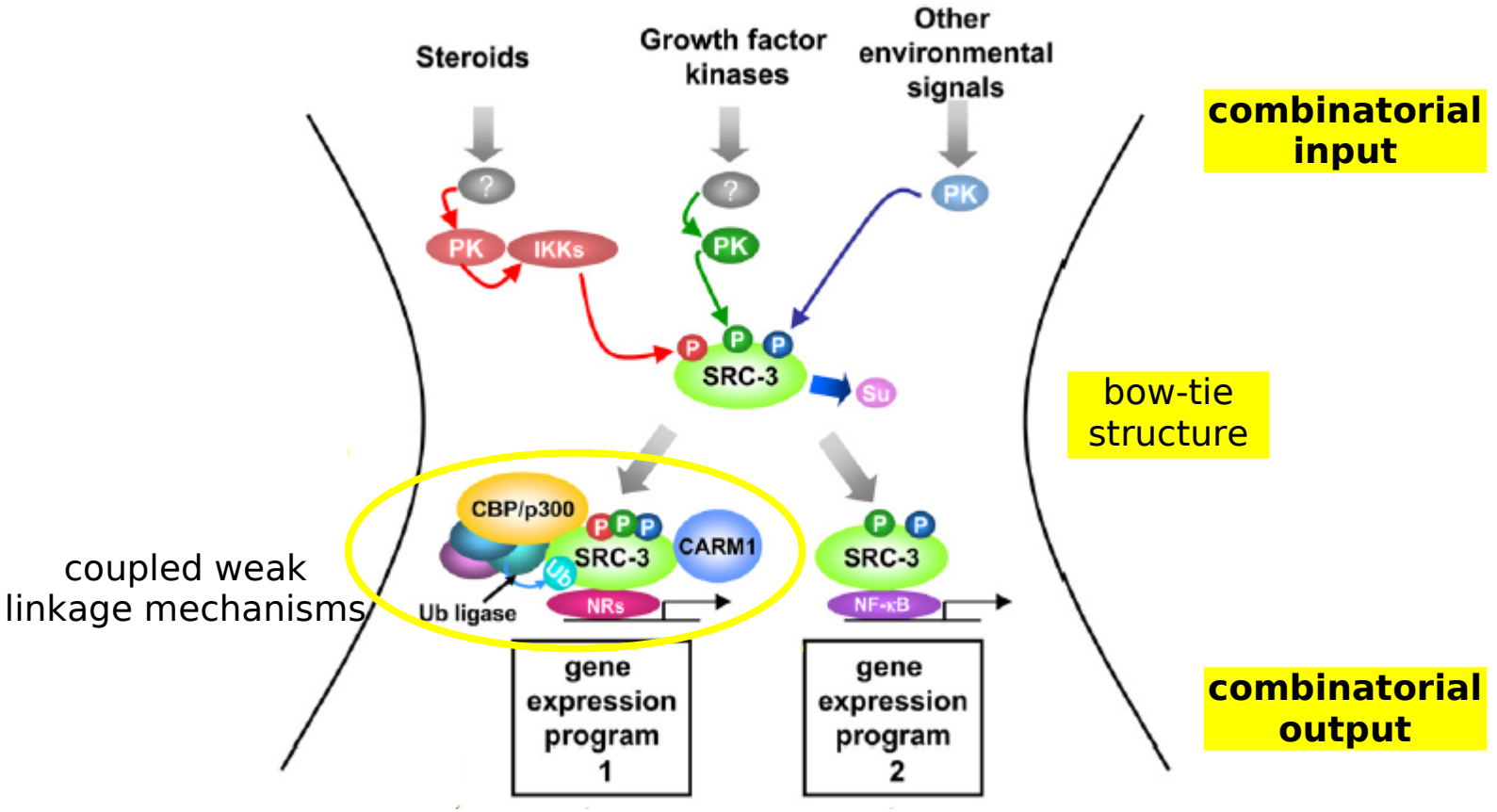




p53

DeHart, Chahal, Flint, Perlman Mol Cell Proteom **13**:1-17 2014

# weak linkage in molecular regulation – PTM

PTMs provide weak linkage through intermediation

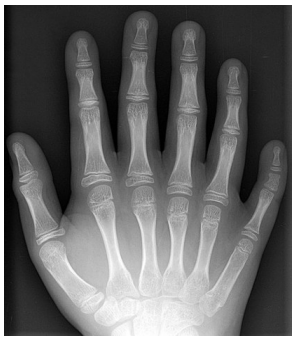



Lonard, O'Malley, *"Nuclear receptor co-regulators: judges, juries and executioners of cellular regulation"*, Development **128**:617-29 2001

Sudhakaran, Lippens, Steen, Gunawardena, *"Post-translational modification: nature's escape from genetic imprisonment and the basis for dynamic information encoding"*, WIRE Syst Biol Med **4**:565-83 2012

# weak linkage in development

**polydactyly** can arise from a mistake during development or through autosomal dominant mutations of variable penetrance. it can sometimes gives rise to a fully functioning finger.



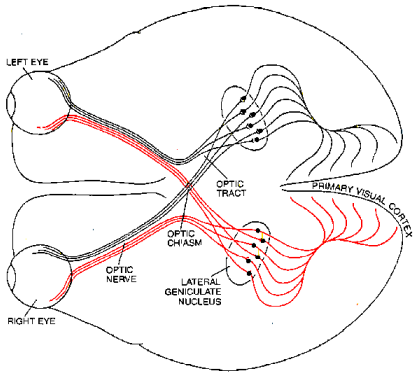
for this to happen, the processes that work to form a finger – bone, muscle, cartilage, vasculature, nerves, ... – must be **weakly linked**

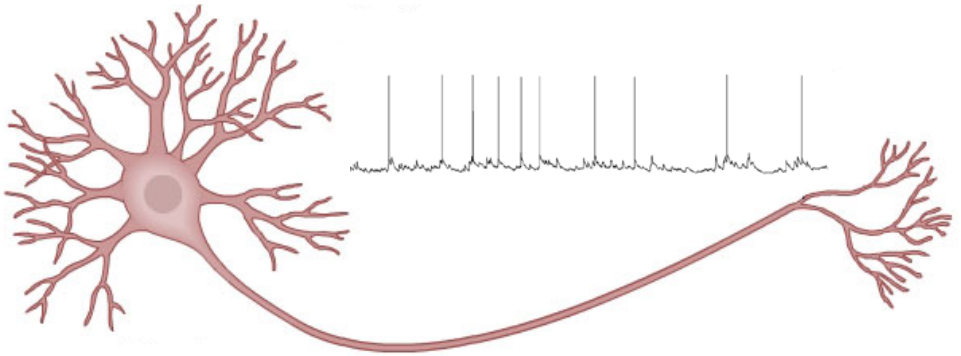
**conjoined twins**

Ladan & Laleh Bijani
1974 - 2003

# weak linkage in development – learning

during organismal development, there is a “critical window” during which neuronal connections are formed in an activity-dependent manner



**weak linkage**: the neurons in the CNS learn from the signals which the eyes send them, thereby extracting new information and enabling a fitness advantage for the organism to arise from mutations which improve the optics of the eye

**101** → **A**

**010** → **?**

**learning**

**101** → **A**

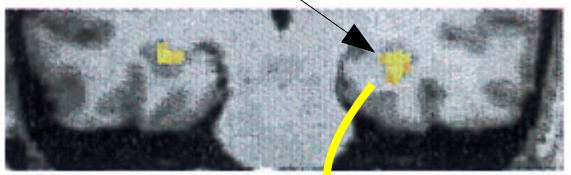
**010** → **B**

David Hubel, **Eye, Brain and Vision**, Scientific American Library, 1988

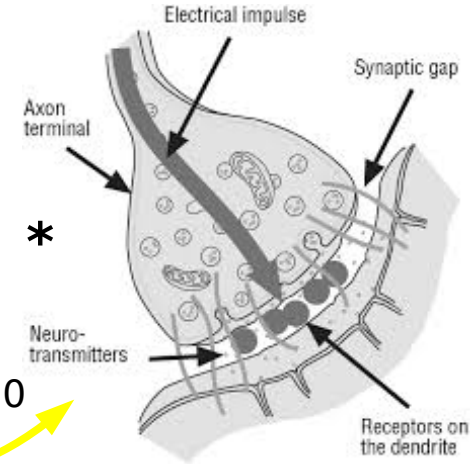
Dale Purves, **Brains: How They Seem to Work**, FT Press, 2010

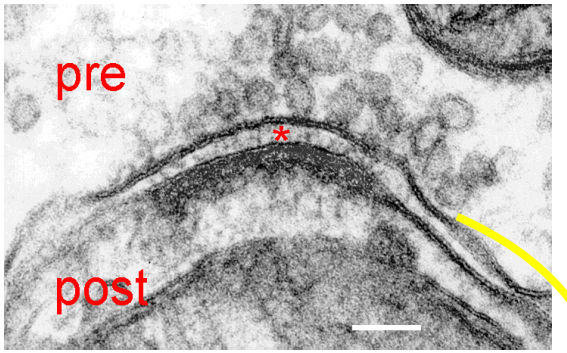
# learning in the brain

hippocampus

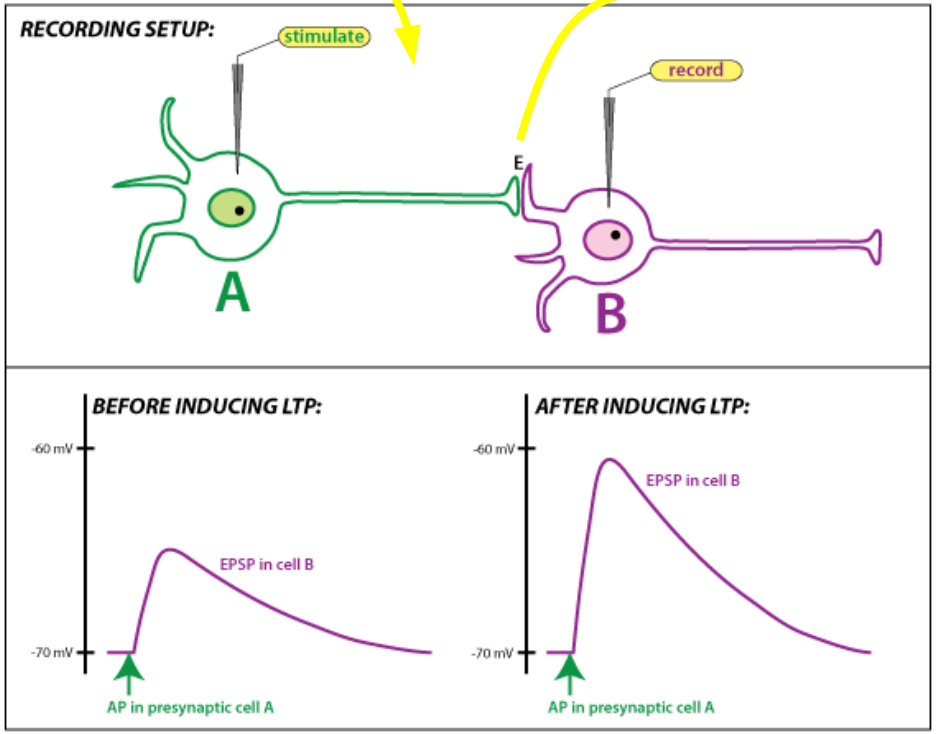


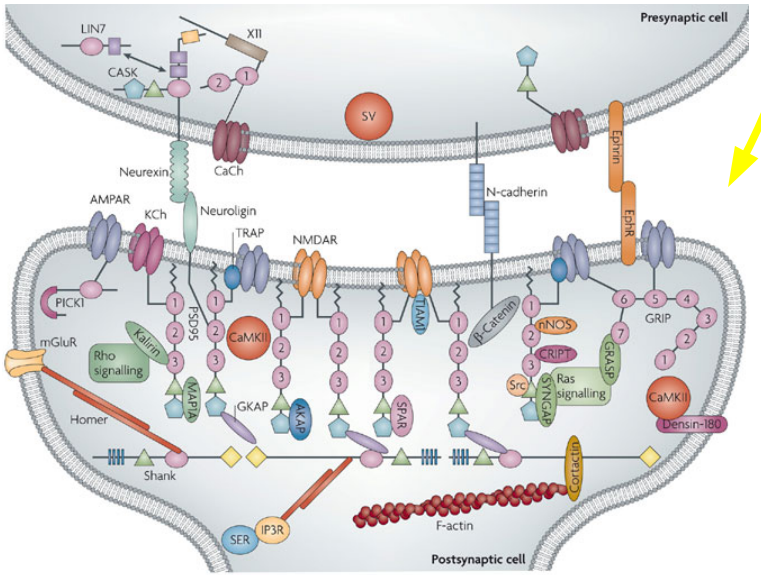
Maguire et al, PNAS 97:4398-403 2000




SynapseWeb @UTexas




Feng, Zhang, Nat Rev Neuro 10:87-99 2009

https://courses.washington.edu/conj/bess/memory/cellular-memory.html

* *http://www.ascd.org/publications/books/104013/chapters/Meet-Your-Amazing-Brain.aspx*

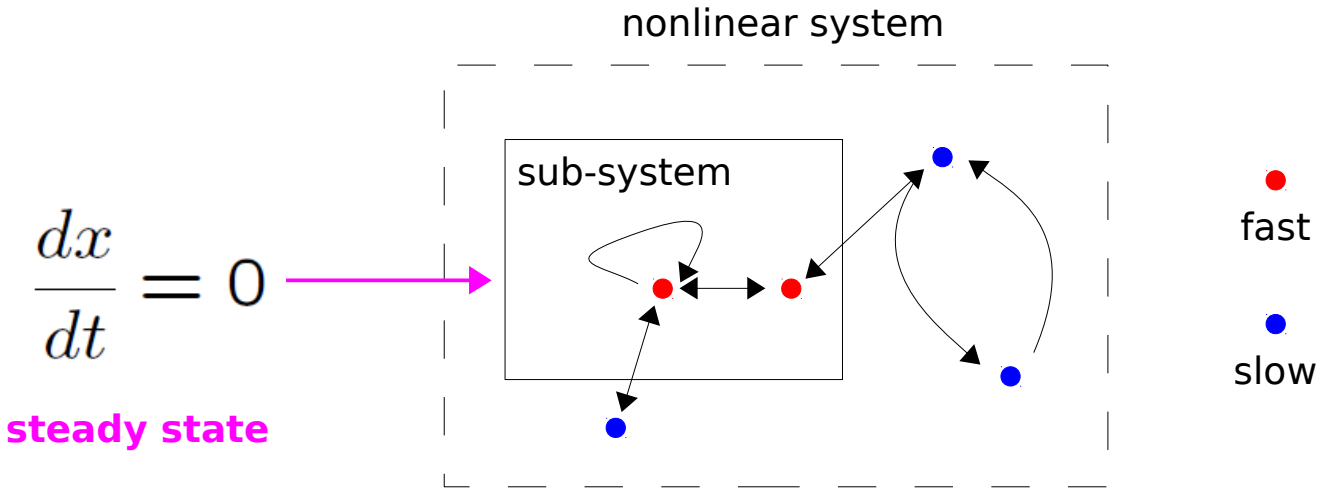
# weak linkage facilitates variation and evolution

- for evolution to give rise to complex organs like the eye, the organism needs appropriate internal mechanisms
- **weak linkage** allows mutations to occur within processes without compromising the organism as a whole, so that mutational change is at least neutral
- this also increases the genetic variation in the population on which positive selection can subsequently act
- weak linkage by intermediation can yield bow-tie structures that are thought to exhibit robustness to perturbations
- in molecular regulation, weak linkage by variation & selection can create enormous amounts of molecular state
- learning, which takes place in the nervous system and perhaps in other physiological systems, is a weak linkage mechanism that allows positive selection to arise, and not just neutrality
- but how did weak linkage mechanisms evolve in the first place ... ?

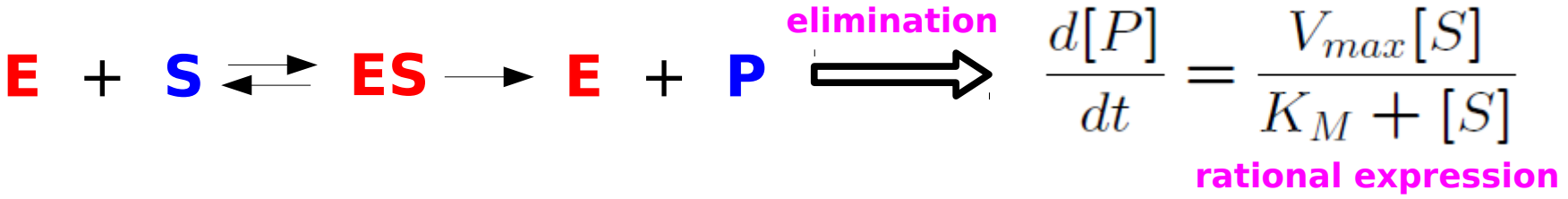
# 3. time-scale separation

# time-scale separation

a sub-system is assumed to be operating sufficiently fast, with respect to the system of which it is a part, that it can be taken to have reached steady state




and the complexity arising from the sub-system can thereby be eliminated

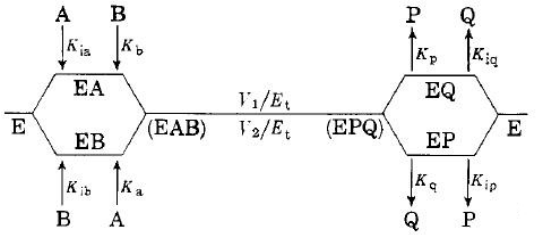



Gunawardena, *"Time-scale separation: Michaelis and Menten's old idea, still bearing fruit"*, FEBS J, **281**:473-88, 2014

# widely used in biology

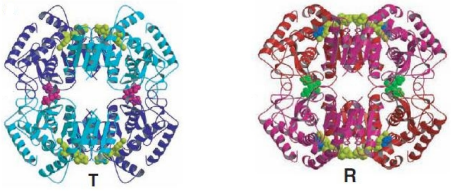
## enzyme kinetics

Gulbinsky & Cleland, Biochemistry **7**:566-75 1968;
King & Altman, J Phys Chem **60**:1375-8 1956



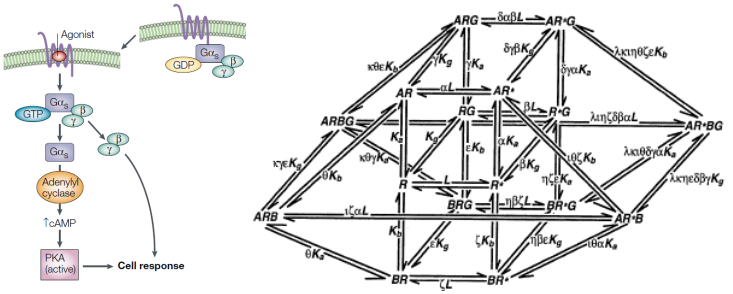

## metabolic regulation

Monod, Wyman & Changeux, J Mol Biol **12**:88-188 1965
Koshland, Nemethy & Filmer, Biochem **5**:365-85 1966



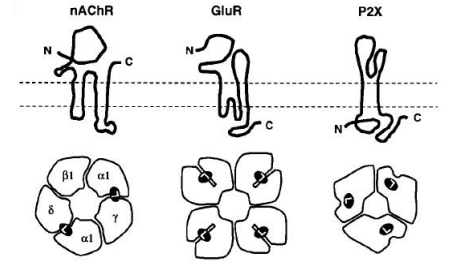

## GPCRs

Samama, Cotecchia, Cost, Lefkowitz, J Biol Chem **268**:4625-36 1993; Christopoulos, Kenakin, Pharmacol Rev **54**:323-74 2002




## ion-channels

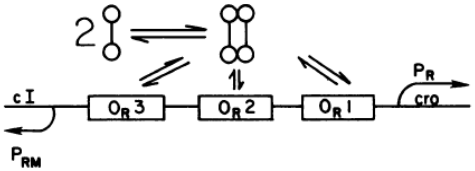
Edelstein, Schaad, Henry, Bertrand, Changeux, Biol Cybern **75**:361-79 1996; Colquhoun, Hawkes, Proc Roy Soc Lond B **211**:205-35 1981



# widely used in biology

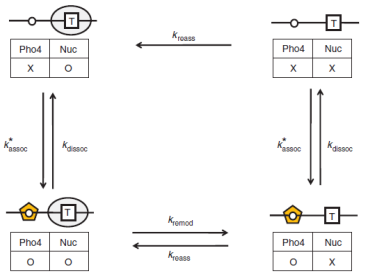
## gene regulation in bacteria

Ackers, Johnson & Shea, PNAS **79**:1129-33 1982



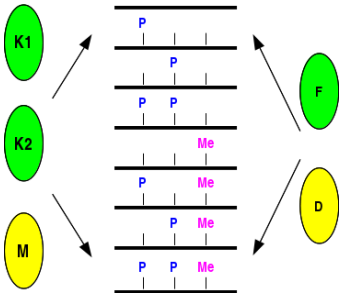

## gene regulation in eukaryotes

Kim & O'Shea, Nature Struct Mol Biol **15**:71192-8 2008




## post-translational modification

Thomson & Gunawardena, Nature **460**:274-7 2009;  9




especially for weak linkage mechanisms that exploit molecular states

## the linear framework

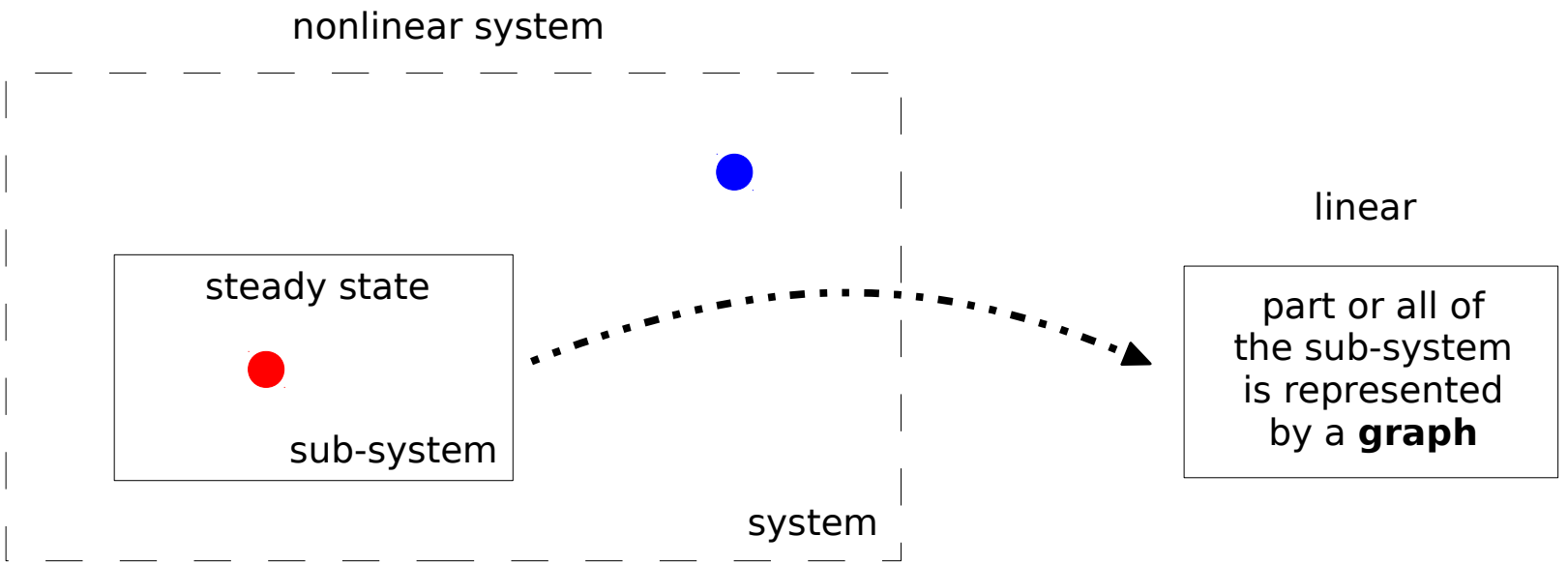
*all these calculations look different and independent*

*in fact, they are all the same calculation*

*and it is a LINEAR one*

Gunawardena, *"A linear framework for timescale separation in nonlinear biochemical systems"*, PLoS ONE **7**:e36321 2012.

# the linear framework




$$E + S \xrightarrow{a} ES$$

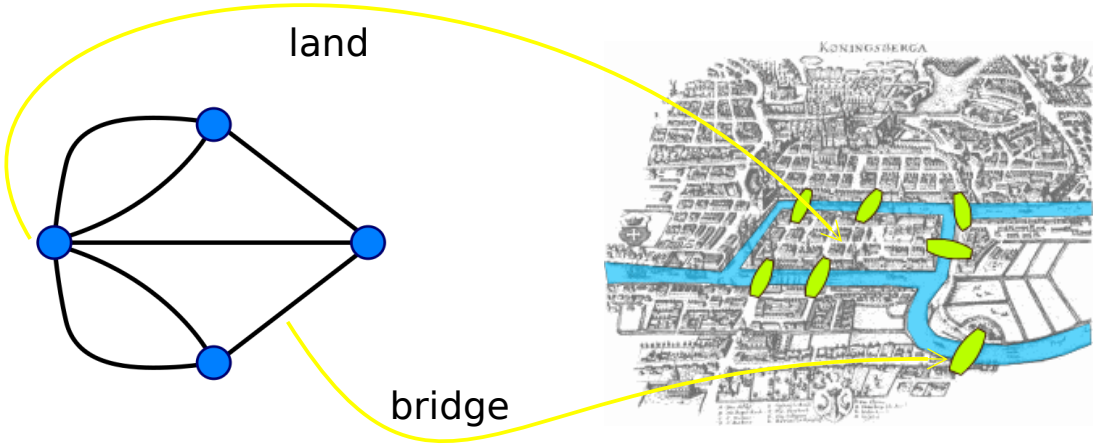
nonlinear reaction with simple rate constants

$$E \xrightarrow{a[S]} ES$$

linear reaction with complex labels

Gunawardena, *"A linear framework for time-scale separation in nonlinear biochemical systems"*, PLoS ONE **7**:e36321 2012; Mirzaev & Gunawardena, "*Laplacian dynamics on general graphs*", Bull Math Biol **75**:2118-49 2013; Gunawardena, *"Time-scale separation: Michaelis and Menten's old idea, still bearing fruit"*, FEBS J **281**:473-88 2014.

# graph theory begins with euler

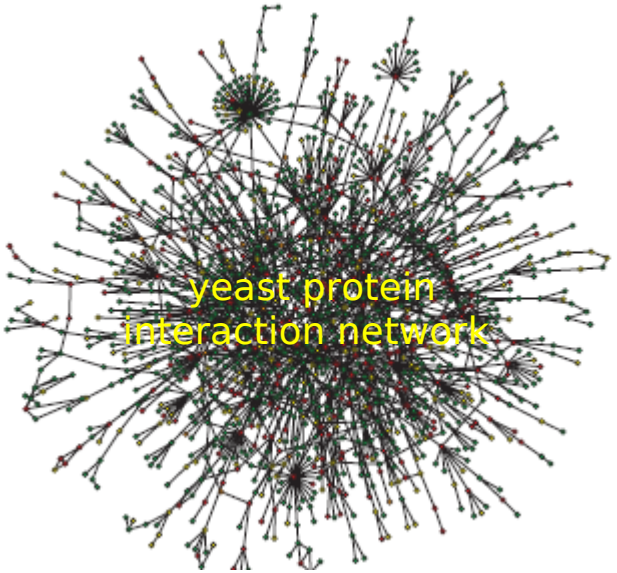



*1707-1783*

Königsberg, modern Kaliningrad

there is no circuit which traverses each edge once and once only (**eulerian circuit**)

graphs are widely used as mathematical representations of biological organisation




Newman "*The structure and function of complex networks*", SIAM Review **45**:167–256 2003; Barabasi, Oltvai, *"Network biology: understanding the cell's functional organization"*, Nature Rev Genetics **5**:101-13 2004.

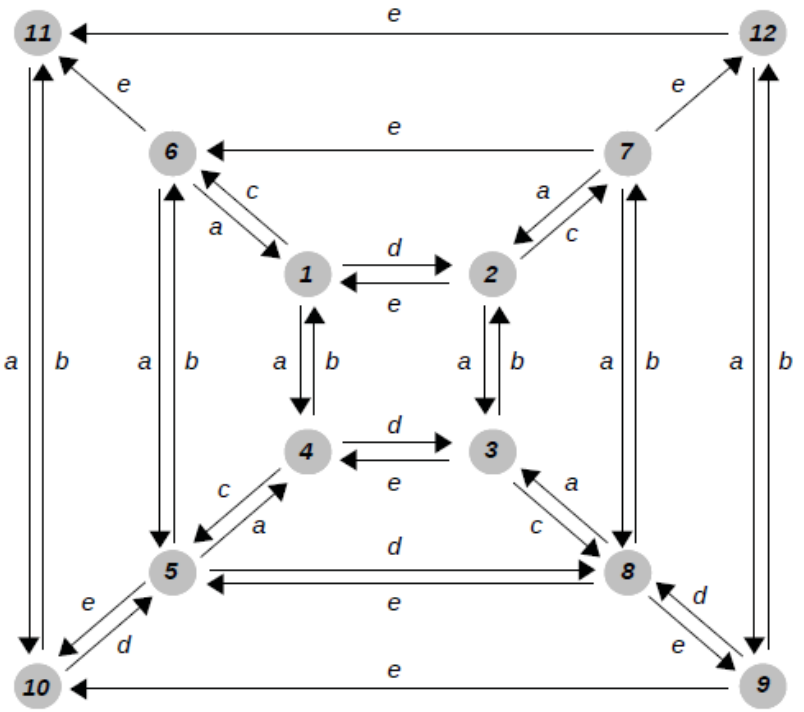
# labelled directed graphs

for the linear framework –

a **graph** consists of **vertices** (or **nodes**), with at most one **edge** between any two distinct vertices

the graph is **directed** – each edge has a specified direction, denoted by an arrow at one end

the graph is **labelled** on each edge

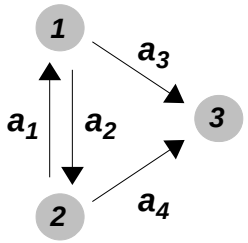



we shall work with graphs which are **connected** (in one piece, forgetting edge directions) and which have **no self-loops**

# Laplacian dynamics – macroscopic interpretation

"one-dimensional" chemistry on graphs

consider each edge as a chemical reaction under mass-action kinetics, with the label as the rate constant




Laplacian matrix

$$\frac{d}{dt}\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} -(a_2+a_3) & a_1 & 0 \\ a_2 & -(a_1+a_4) & 0 \\ a_3 & a_4 & 0 \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

$G$

$$\frac{dx}{dt} = \mathcal{L}(G).x$$

system of linear ODEs

conservation law:

$$x_1(t) + x_2(t) + \cdots + x_n(t) = x_{tot} \qquad 1.\mathcal{L}(G) = 0$$

Gustav Kirchhoff, *"Uber die Auflosung der Gleichungen, auf welche man bei der Untersuchung der linearen Verteilung galvanischer Strome gefuhrt wird"*, Ann Phys Chem, **72**:497-508 1847

# Laplacian dynamics – microscopic interpretation

let $X(t)$ be a time-homogeneous **Markov process** on the states $1, \cdots, n$ for which **infinitesimal transition rates** exist –

$$\lim_{\Delta t \to 0} \frac{\Pr(X(t+\Delta t) = i \mid X(t) = j)}{\Delta t} = a_{ij}$$

define the graph, $G_X$ , with vertices $1, \cdots, n$ and an edge $j \to i$ iff $a_{ij} \neq 0$ give this edge the label $a_{ij}$

the **stochastic master equation** (Kolmogorov forward equation), for the probability of $X(t)$ being in state i at time t, is identical to Laplacian dynamics on $G_X$

$$x_i(t) = \Pr(X(t) = i) \qquad \boxed{\frac{dx}{dt} = \mathcal{L}(G_X).x}$$

Mirzaev & Gunawardena, Bull Math Biol **75**:2118-49 2013

# basic facts

for any graph, G, Laplacian dynamics always tends to a stable steady state

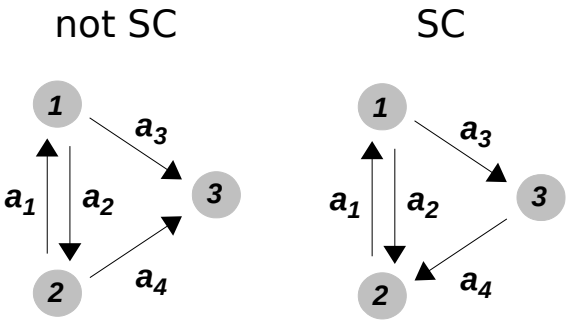
$$x(t) \to x^* \qquad \left.\frac{dx}{dt}\right|_{x=x^*} = 0 \qquad x^* \in \ker \mathcal{L}(G)$$

if G is **strongly connected**, the steady state is unique up to a scalar multiple

$$\ker \mathcal{L}(G) = \langle \rho \rangle$$

where a basis element, $\rho$ , can be calculated in terms of the labels (see later)

**strongly connected** – there is a directed path between any two distinct vertices




Mirzaev & Gunawardena, Bull Math Biol **75**:2118-49 2013